

The prevalence of diabetes is increasing globally and India is no exception. The lifestyle modification and drug intervention are likely to delay or postpone the development of overt diabetes in persons diagnosed to have impaired glucose tolerance. This is a post primary prevention strategy. The primary prevention is more important as this effort is likely to reverse or halt the epidemic of disease. Women with Gestational Diabetes Mellitus (GDM) are an ideal group for the primary prevention of diabetes as they are at increased risk of future diabetes, predominantly type 2 diabetes, as are their children. Pima Indians have the highest prevalence of diabetes. This is attributed to the children exposed in utero to maternal diabetes. Hence as a policy to identify GDM and its consequences on the infant, a 75gm Oral Glucose Tolerance Test has been recommended to all Pima Indian women during the 3<sup>rd</sup> trimester of pregnancy. Ethnically Asian Indian women also have high prevalence of diabetes and the relative risk of developing Gestational Diabetes Mellitus in them is 11.3 times compared to White women. This necessitates universal screening for gestational diabetes during pregnancy in India. Probably the undiagnosed gestational diabetes that has been occurring in the past has resulted in the increased prevalence of diabetes in India. The timely action taken now in screening all pregnant women for glucose intolerance, achieving euglycemia in them and ensuring adequate nutrition may prevent in all possibility, India becoming the diabetes capital of the world.

The prevalence of diabetes is increasing globally and India is no exception. The concern is that India would be having the highest population of diabetes by 2025.<sup>1</sup> The increased prevalence is attributed to the aging population structure, urbanization, the obesity epidemic, and physical inactivity. While all these factors contribute to the epidemic of diabetes, early life exposures are emerging as potential risk factors. The “fetal origin of disease” hypothesis proposes that gestational programming may critically influence adult health and disease. Gestational programming is a process whereby stimuli or stresses that occur at critical or sensitive periods of development, permanently change structure, physiology, and metabolism, which predispose individuals to disease in adult life. Traditionally and convincingly, lifestyle modifications and drug interventions have proved to delay or postpone the development of overt diabetes in persons diagnosed to have impaired glucose tolerance. This is a post primary prevention strategy. The primary prevention of Type 2 DM at best would mean to keep genetically or otherwise susceptible individuals

normoglycemic and not only preventing Type 2 DM from developing. The primary prevention is more important than post primary prevention, as this effort is likely to reverse or halt the epidemic of disease. Women with Gestational Diabetes Mellitus (GDM) are an ideal group for the primary prevention of diabetes as they are at increased risk of developing diabetes predominantly Type 2 DM as are their children.

Gestational Diabetes Mellitus is defined as carbohydrate intolerance of variable severity with onset or first recognition during the present pregnancy. Women with GDM have an increased lifetime risk of developing diabetes, at over 3 times compared to controls at 16 years after index pregnancy. By 17 years of age one third of children born to GDM mothers have had evidence of IGT or Type 2 DM. In our ongoing community based project sponsored by World Diabetes Foundation, 33% of the women who developed GDM had maternal history of diabetes. The familial predisposition to type 2 diabetes mellitus is mediated by both genetic and intrauterine environmental factors. The contribution of the genetic factor may be due to the major role played by maternal mitochondrial DNA in the transmission of disease. The ovum is well supplied with mitochondria but the sperm contains a few and even those few do not persist in the offspring. At fertilization, it is the nucleus of the spermatozoan that enters the ovum and thus all the cytoplasm, mitochondria and mitochondrial DNA are exclusively maternally inherited. Maternal inheritance is attributed to mutation in the gene(s) present on mitochondrial DNA and is transmitted invariably by an affected mother to her progeny. However studies have also shown, low genetic risk for diabetes, exposure to hyperglycemia in utero significantly increases the risk of diabetes in adult life.

Yet another study revealed that children exposed in utero to maternal diabetes are at a higher risk of obesity and diabetes than their unexposed siblings, suggesting that the increased risk to the exposed offspring is not exclusively genetic. These observations clearly indicate the need to focus on the intra uterine environment. The maternal fuels glucose, amino acids and lipids (mixed nutrients) which are in excess in women with glucose intolerance due to decreased insulin secretion or action, cross the placenta and stress the fetal beta cells. The fetus responds to the mixed nutrients by secreting large quantities of insulin. This results in increasing adiposity and accrual of visceral fat that eventually causes decrease in fetal pancreatic reserve and the infant is at risk for developing

740 subsequent diabetes. On the other hand, intrauterine malnutrition causes intrauterine growth retardation and this under nutrition is associated with decreased pancreatic reserve. Thus both small for dates infants and large for dates infants are at risk for subsequent diabetes. In India, both under nutrition and over nutrition exist during pregnancy.

There are two reported studies in India which are related to the size at birth to future risk of Type 2 diabetes. In Mysore, low birth weight did not increase the risk of diabetes but babies who were short and fat (higher body mass index, BMI) at birth were at increased risk.<sup>16</sup> Fall *et al* speculate that the rise in Type 2 diabetes in Indian urban populations may have been triggered by mild obesity in mothers, leading to glucose intolerance during pregnancy, macrosomic changes in the fetus and insulin deficiency in adult life. Yet another study by Yajnik *et al* attributes high prevalence of Type 2 DM and IGT in Indian people may be linked to poor fetal growth.<sup>17</sup> Same author also suggests that Type 2 DM in India may be programmed in fetal life, hence diabetes prevention will have to start in early life (in utero) and continue in later life. The importance is that the intrauterine milieu, whether one of nutritional deprivation or one of nutritional plenty, results in changes in pancreatic development and peripheral response to insulin that may lead to adult onset GDM and Type 2 DM. The aim should be to help the pregnant women to have infants born with weight appropriate for gestational age (AGA) by adequate and appropriate nutrition and maintaining fasting plasma glucose < 90mg and peak plasma glucose < 120 mg.

In Pima Indians, the population with the highest known rate of diabetes, a study found that the increased exposure to diabetes in utero and childhood obesity accounted for most of the increased prevalence of diabetes over the past 30 years. If the diabetic intrauterine environment is substantially contributing to the obesity and diabetes epidemics, populations that have a high prevalence of diabetes will continue to be disproportionately affected by these epidemics, resulting in a perpetual widening of health disparities between racial and ethnic groups.

It is imperative to understand the trans generational epidemiology and etiology of diabetes and develop simple, economical, and effective prevention strategies. These observations call for the screening for the glucose intolerance during pregnancy and ensuring adequate nutrition for the developing fetus. The WHO criteria of 2h PPG > 140 mg/dl identifying a large number of cases may have a greater potential for prevention and is being followed in many parts of the world. The screening for glucose intolerance is usually performed around 24 – 28 weeks of gestation. But a statistically significant number of GDM mothers deliver big babies despite good glycemic control in the third trimester. This is due to the undetected glucose intolerance in them in the early weeks of gestation that influences the fetal growth. Fetal pancreatic islets of Langerhans differentiate during the 10th and 11th week

of development and begin to release insulin in response to nutrients as early as 11th – 15th weeks of gestation. The priming of the beta cell mass in early gestation may account for the persistent fetal hyperinsulinemia throughout pregnancy and the risk of accelerated growth, even when the mother enjoys good metabolic control in later pregnancy. Alterations of intrauterine environment in particular, the development of hyperinsulinemia is strongly associated with the development of obesity and IGT during childhood and puberty. 'Early maternal metabolic imprint may affect the fetal growth'. This observation implies that screening is to be performed in the first trimester itself as the fetal beta cell recognizes and response to maternal glycemic level as early as 16 th week of gestation.

The criteria recommended by WHO is simple and cost effective and is practiced in many centers. But the pregnant woman has to be in the fasting state. Asking a pregnant woman to come in the fasting state is impractical in many settings due to long distance of travel to reach the health centers for the test. Besides pregnant woman does not want to be in the fasting state for long hours as she believes that fasting is not good for her fetus. International association of diabetes in pregnancy study group (IADPSG), recommends that GDM can be diagnosis if any one value meet or exceed FPG 92mgs, 1hr 180mgs and 2hr pg 153mgs with 75g of oral glucose load. This procedure also impractical as it is not cost effective and the pregnant women has to be in the fasting state. To overcome all this practical problems A single step procedure of diagnosing GDM with 2hr pg > 140mgs after oral administration of 75g glucose to a pregnant women in the fasting or non-fasting state, irrespective of the last meal timing was introduced. This procedure has been validated by a number of studies and Diabetes and pregnancy study group in India has accepted this procedure. Ministry of health govt of India, WHO and International association of gynaecologists and obstetricians (FIGO) have also accepted this procedure for diagnosing GDM.

Over the next 2 to 3 decades there will be 80 million reproductive age women with diabetes in the world. Of these 20 million will live in India alone creating a potential for extremely high rates of maternal and infant morbidity. Women who had GDM, develop overt diabetes at a young age, substantially increasing their lifetime risk of developing complications from diabetes.

In conclusion, increasing maternal hyperglycemia is associated with increasing pregnancy morbidity and increased likelihood of subsequent diabetes in the mother. In addition, maternal hyperglycemia has a direct effect on the development of fetal pancreas and is associated with increased susceptibility to future diabetes in the infant an effect which is independent of genetic factors. Among ethnic groups in South Asian countries, Indian women have the highest frequency of GDM necessitating universal screening for glucose intolerance during pregnancy in India. Probably the undiagnosed glucose intolerance that has been occurring in the past

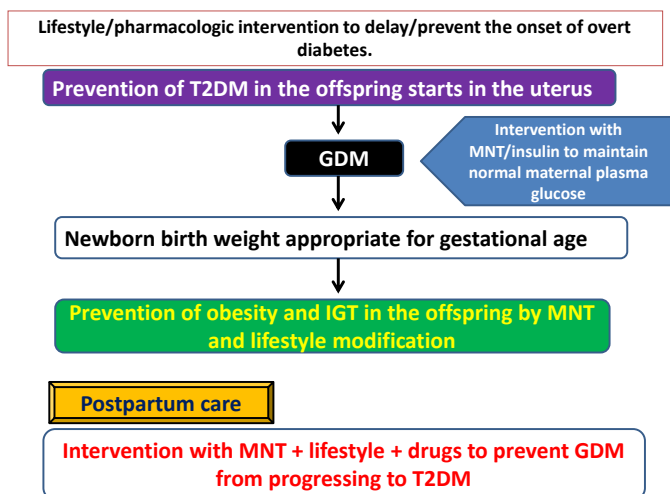


Fig. 1

has resulted in the increased prevalence of diabetes in India. Moreover, women who have GDM, because of their high diabetes risk and young age, are ideally suited to be targeted for lifestyle or pharmacologic interventions to delay or prevent the onset of overt diabetes.

Hence, an important public health priority is prevention of diabetes, starting with maternal health pre and post conception. Preventive measures against Type 2 DM should start during intra uterine period and continue throughout life from early childhood. The timely action taken now in screening all pregnant women for glucose intolerance, achieving euglycemia in them and ensuring adequate nutrition may prevent in all probability, the vicious cycle of transmitting glucose intolerance from one generation to another.

## REFERENCES

1. Text book of Diabetes and Pregnancy Edited by Moshe Hod, Lois Jovanovic, Gian Carlo Di Renzo, Alberto, Oded Langer. Published by MD Martin Dunitz Taylor & Francis Group Plc 2003